ARGUMENTS

By the foregoing amendment, claim 1 has been amended to correct a typographical error and to specify that the compound is administered at a dose that effectively deters, inhibits or reverses stenosis, restenosis or unwanted proliferation of an artery but does not inhibit hepatic cytochrome P450 enzyme activity. Support for this amendment is found in the specification, such as at Page 8. No new matter has been added. Reconsideration is respectfully requested.

35 U.S.C. §112 Rejections

In the Office Action, claims 1-16 were rejected under the first paragraph of 35 U.S.C. §112 on grounds that, although the specification is "enabling for deterring, inhibiting, or reversing stenosis, restenosis or unwanted proliferation of an artery" it is not enabling for "preventing" such processes.

By the forgoing amendment, the word "preventing" have been removed from the preamble of claim 1, thereby overcoming this stated rejection under 35 U.S.C. §112 .

35 U.S.C. §103 Rejections

In the Office Action, claims 1-16 were also rejected under 35 U.S.C. §103 as being obvious over United States Patent No. 5,358,959 (Halpern) in view of United States Patent No. 6,803,375 (Chandy et al.) and further in view of United States Patent No. 6,613,083 (Ault).

Halpern et al. teaches the use of imidazole compounds, including clotrimazole, for the treatment of atherosclerosis, inhibiting unwanted endothelial and smooth muscle proliferation and for delaying or avoiding restenosis. Halpern et al. fails to teach the presently-claimed compounds. However, the Examiner has maintained the contention that Chandy et l. teaches that "preferred compounds possess the same activities to inhibit endothelial cells" and that "one skilled in the art would have assumed that the substitution of another compound that possesses the same activity would achieve the same results in the absence of evidence to the contrary." Applicant respectfully disagrees with this reasoning. Furthermore, as now amended, independent claim 1 requires the compound to be administered at a dose that effectively deters, inhibits or

reverses stenosis, restenosis or unwanted proliferation of an artery but does not inhibit hepatic cytochrome P450 enzyme activity.

As explained in the specification of the instant application, Applicant has discovered that, unlike clotrimazole, compounds of the present invention can be administered at doses that effectively deter, inhibit or reverse stenosis, restenosis or unwanted proliferation of an artery but do not inhibit hepatic cytochrome P450 enzyme activity. These unforeseen results are not obvious from the prior art.

Moreover, simply because a compound is capable of inhibiting Ca++ activated potassium channels does not mean that the same compound would be capable of deterring, inhibiting or reversing stenosis, restenosis or unwanted proliferation of an artery *and* doing so at a dose that does not also cause significant cytochrome P450 inhibition.

Indeed, Halpern et al. would not lead any person of skill in the art to assume that, simply because certain imidazole compounds that inhibit Ca++ activated potassium channels were also found to have activity against restenosis or atherosclerosis, other classes of compounds that inhibit Ca++ activated potassium channels would *also* have the same activity against restenosis or atherosclerosis. To the contrary, Halpern et al. actually teaches away from such assumption. Specifically, at column 3, lines 55 through 63, Halpern et al. states as follows:

> Other specific inhibitors of the Ca++ activated potassium channel (such as charybdotoxin, caliotoxin and iberotoxin) do not inhibit proliferation of endothelial or vascular smooth muscle cells. Moreover, inhibitors of other transport systems that are activated by mitogens, such as ouabain (highly specific inhibitor of the Na/K pump) and amiloride (inhibitor of Na/H exchange) do not inhibit cell proliferation. Thus, the results obtained by the inventor are surprising.

The law requires that Halpern et al. be considered in its entirety, i.e., as a whole, including the above-quoted portion that clearly teaches away from any expectation or probability that Applicant's claimed compounds would be effective for the treatment of stenosis, restenosis or unwanted proliferation of an artery. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

In view of the express teaching by Halpern et al. that not all inhibitors of Ca++ activated potassium channels inhibit proliferation of endothelial or vascular smooth muscle cells, there would have been no basis to predict with reasonable certainty that the compounds disclosed by Chandy et al. would be effective for the presently claimed methods. Such predictability of the outcome is a necessary component of any finding of obviousness. In this regard, United States Supreme Court has stated in *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. at 1, 82 USPQ2d at 1391 (2007) that:

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability.

Thus, Applicant's presently claimed method for treatment of stenosis, restenosis or unwanted proliferation of an artery id not obvious over Halpern et al. in view of Chandy et al.

Alt is relied upon only for teaching the concept of coating of stents for implantation. Alt describes a coated stent that delivers an effective dose of the immunosuppressant drug tacrolimus to the vessel wall. The tacrolimus is purportedly delivered at a rate and in a concentration that both encourages proliferation of smooth muscle cells and limits conversion of such cells to the secretory type muscle cells. Alt ads nothing to cure the deficiencies of the Halpern et al./Chandy et al. combination as basis for the stated obviousness rejection.

Conclusion

For the foregoing reasons, Applicant believes that claims 1-16 are in condition for allowance and should be passed to issue. No fee is seen to be due in connection with the filing of this response. However, in the event that a fee is properly deemed to be due, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 50-0878.

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Respectfully submitted,
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